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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

THE SENSITIVITY OF GUINEA PIGS TO PENICILLIN¹
(Preliminary Report²)

Z. f. Haut. u. Gesellsch. Krankheiten 11: 210-15, 1953

H. Grimmer

Publications dealing with the pharmacologic or toxicologic effects of penicillin in animals frequently note that, in contrast to all other laboratory animals, guinea pigs (G.P.) show relatively little tolerance to this antibiotic. Interpretation of this phenomenon is difficult, the underlying mechanism being complex in nature. Koch, Heiss and Schneider observed that after a single dose of 8 to 12 Mega Na-penicillin/kg in G.P. a weight loss of 8 to 24 percent occurred after several days, the autopsies showing severe toxic enteritis to be the dominant symptom of the intoxication. These workers believe that the low tolerance was due to lack of "penicillinase activity." In contrast to conditions in the rat, in the brain of G.P. penicillin (Pc.) was observed which could cause stimulation of the vegetative system, and, at appropriate dose and duration of action, could lead to circulatory disturbances, especially in the intestinal wall, and therefore to development of enteritis.

The tolerance of the animals in the toxicologic studies of Miescher and Bohm was even smaller, since in one experimental group of 20 G.P. after a single i.c. (expansion not known, perhaps means intercutaneous) injection of 33,000 U/kg, 12 animals died after 24 hours, 3 after 3 days and 3 more animals after 7 days. In another experimental group the tolerable dose was only 200 U/kg. Upon increasing the injected amount the death rate rose rapidly since, when using crystalline penicillin of various origins, 20 out of 22 animals died within 2 to 7 days.

During study of the conditions underlying Pc. intolerance in G.P., we observed a heretofore unnoticed nutritive factor which became

apparent when P_c. tolerance was observed to be dependent in a significant and regular manner upon the supply of green fodder (cauliflower leaves). The findings of these investigations will be reported in detail elsewhere; we confine ourselves herein to an abridged summary with illustrative curves.

ANIMAL EXPERIMENTAL STUDIES: (3)

All animals used in the following experiments were bred by us and were either colored or albino. The quantities of penicillin listed in the curves were given daily subcutaneously. The autopsy and pathohistologic findings in those animals which died during the experiment will likewise be reported elsewhere.

EXPERIMENTAL STUDIES:

Group A (7 animals weighing 125 to 210 grams, 2 weighing 260 to 330 grams, 3 weighing 410 to 500 grams).

This group, receiving a complete diet (oats, hay, green fodder), was treated with increasing doses of penicillin, i.e., 6 days at 1000 U/kg, 7 days at 2000 U/kg, 8 days at 6000 U/kg, 8 days at 8000 U/kg, 4 days at 10,000 U/kg and 3 days at 20,000 U/kg of crystalline-Pc. Following this we changed over to depot-Pc, and in fact, for 7 days the animals received 20,000 U/kg, followed by 11 days at 40,000 U/kg, 7 days at 80,000 U/kg, 11 days at 100,000 U/kg, 6 days at 200,000 U/kg and are now being treated with 400,000 U/kg.

RESULTS:

Table I shows that the shape of weight curves during P_c. treatment is dependent upon the initial weight of the animals, in so far as younger animals show a more marked growth rate than older animals and a correspondingly greater weight gain. In passing from 10,000 to 20,000 U/kg of crystalline P_c., only in the light group (125 to 210 grams) was an insignificant weight loss (3% within 8 days) noticeable, while the other weight categories showed further but slightly retarded weight gain. On days 49, 50, 52 and 53, green fodder was withheld with the result that on the third day of omission a sudden drop in weight occurred in all animals which was rapidly compensated by renewed feeding with green fodder, even though the daily penicillin dose was increased. Only one animal which had suffered injury from green fodder withdrawal died.

The lowest weight group withstood the high dosages without complications while increasing in weight; the middle weight group after

a period of weight loss gained again; only the heavy group showed a tendency to lose weight. All animals were clinically healthy during the experiment, had normal pelt and appetite, no diarrhea and no tissue damage at the site of injection.

Group B (13 animals weighing 130 to 260 grams).

This group, represented as a homogenous ensemble, received its first penicillin injection when its average, though relatively minimal, weight had reached about 165 grams. The initial dose amounted to 2000 U/kg and, as can be seen in Table 2, was continually increased to 20,000 U/kg of depot Pc. by the fortieth day and was raised after another 14 days to 40,000 U/kg.

RESULTS:

All animals showed weight increases under increasing penicillin administration until such time as green fodder was eliminated from the food for a 4 day period (the 40th, 49th, 51st and 52nd experimental day). In analogy with Group A, it was found that two days' of omission of green fodder is continued without change occurring in the weight curve and only on the third day does a rapid fall in the regular curve (-20%) result, which, with continuation of the daily Pc.-injection and renewed feeding of green fodder, returns to normal after 11 days. Despite doubling of the penicillin dose (40,000 U/kg depot Pc) growth increased until the day that green fodder was permanently eliminated. Up to this time only one animal succumbed because of toxic symptoms after its weight was only 25% above starting weight. The result of the fodder-free diet was that within 13 days, 9 animals perished. The 4 surviving animals continued to lose weight so that it may be assumed they will succumb in the near future.

Group C (7 animals weighing 210 to 260 grams, 4 animals weighing 300 to 450 grams).

The dosage, with respect to the amount of crystalline-Pc. was the same as in Group A. Commencing on the forty-third experimental day, 20,000 U/kg depot-Pc. was administered for 28 days; during this period there were 19 fodderless days. On day 66, green fodder was again given and after day 70 a dose of 100,000 U/kg was administered.

Table 3 shows that weight increased continuously from the start of the experiment, only on day 3 of the green fodder-free diet period, as in Groups A and B, there was a critical fall in weight, to which one animal succumbed under toxic effects of penicillin. Upon supplementing the diet with oatmeal gruel, a transient increase in weight was obtained (replacing the water loss?) which was, however, rapidly

Table 1. Group A

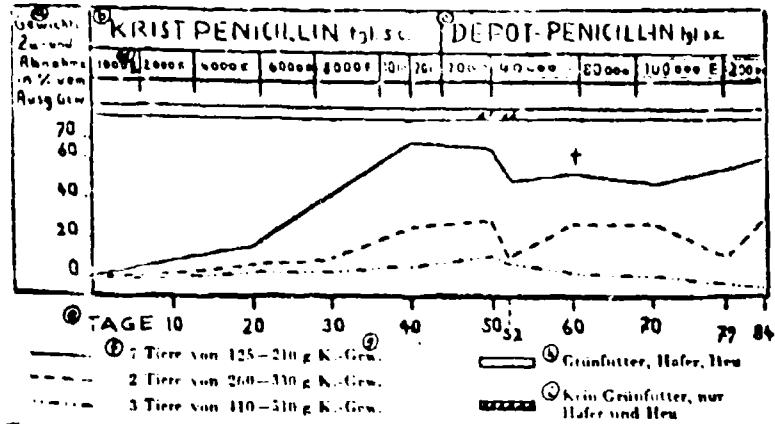
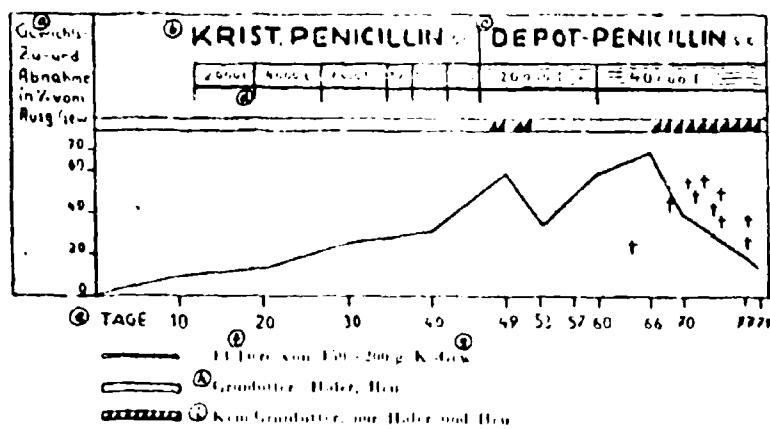


Table 2. Group B



[Legend]: a) Weight gain and loss or % initial weight; b) Crystalline penicillin daily S. C.; c) Depot - penicillin daily S. C.; d) E = U (Unit); e) Days; f) animals; g) body weight; h) green fodder, oats, hay; i) no green fodder, only oats and hay.

followed by a new fall in the younger group, while the older group showed a retardation in weight gain. On restarting, the green fodder diet led to a rapid weight increase in the younger group and to a gradual increase in the older, even though the dosage schedule was modified from that of Groups A and B in so far as in this group the dose of penicillin was raised from 20,000 to 100,000 U/kg.

Group D (2 animals weighing 400 to 500 grams, 2 animals weighing 410 to 510 grams, 3 animals weighing 650 to 750 grams).

The purpose of this experiment was the clarification of the questions raised by the first three experiments: whether the penicillin tolerance which appeared under green fodder omission is not merely the consequence of a possible lack of Vitamin C.

Table 4 shows that a higher starting dose (8,000 U/kg crystalline-Pc.) is met by the heavier animals with an initial weight loss of about 10%. Two animals died on days 7 and 8 of the experiment; the remaining 5 animals gained, even at a dosage of 20,000 U/kg depot-Pc.; only upon eliminating the green fodder did rapid weight loss occur (within 18 days, 20 or 36 percent). One animal died on the sixteenth day of the fodder-free period, another perished after the diet was again supplemented with the fodder, while the remaining 3 regained during the course of the 6 green fodder days (25 percent), only to lose once more when the green fodder was again withdrawn. As can be seen from Table 4, Vitamin C, even in manifold overdosage (100 mg per animal) could not compensate for weight loss caused by omission of green fodder.

It should be noted that application of penicillin during the green fodder-free days resulted in a continuous disturbance, such that the animals, after withholding green fodder starting with day 54 and with no penicillin treatment, showed relatively severe weight loss. It should be recalled, however, that the older animals have a reserve of weight at their disposal and therefore in dropping to a fixed minimum weight, either do not succumb or do so less rapidly than when under simultaneous penicillin treatment.

DISCUSSION:

The preceding studies provide an insight into the significance of nutritive factors in the pathogenesis of toxic effects of penicillin. In practice, elimination of green fodder (cauliflower leaves) leads to a reduction in penicillin tolerance which is, however, not solely due to a lack of Vitamin C, since even manifold overdosage of ascorbic acid does not compensate the complex of toxic symptoms which develops through omission of green fodder. It can be surmised that cabbage leaves contain specific effective substances which, for the moment, we shall hypothetically designate as the "cabbage factor," which are

Table 3. Group C

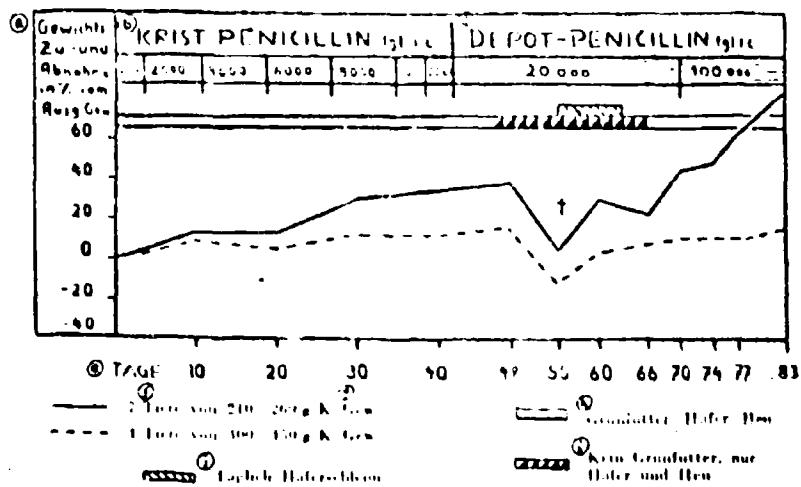
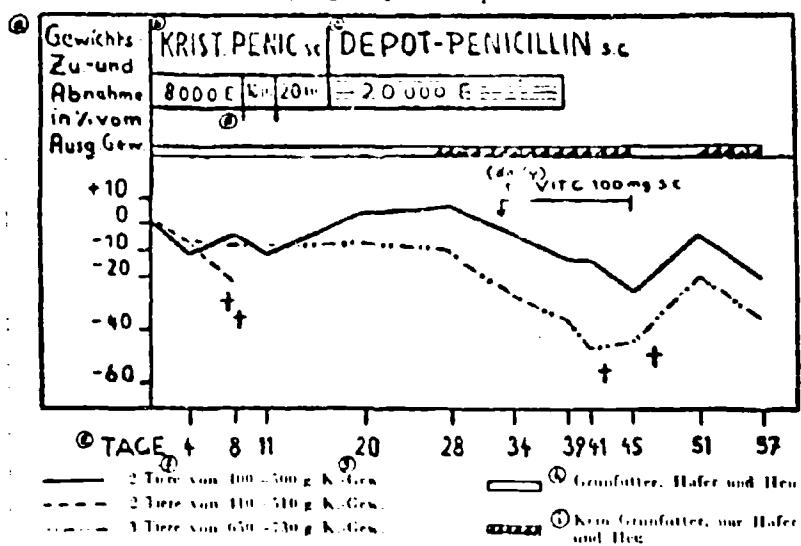


Table 4. Group D



[Legend]: a) Weight gain and loss or % initial weight;
b) Crystalline penicillin daily S. C.; c) Depot - penicillin daily S. C.; d) E = U (unit); e) Days; f) animals; g) body weight; h) green fodder, oats, hay;
i) no green fodder, only oats and hay; j) daily oatmeal gruel.

able to raise the limit of tolerance of guinea pigs towards penicillin. Tissue water deprivation caused by withdrawal of green fodder cannot in itself be decisive since the addition of fluids in the form of oatmeal gruel causes only a temporary increase in weight which is again followed by weight loss. The investigations are being continued and we are now attempting to determine whether a disturbance in adrenal functions plays a role in the pathogenesis of the toxic effects of penicillin.

REFERENCES:

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pages 1-8

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FOOTNOTES:

(1) Dedicated to the 70th birthday of Professor L. Arzt.

(2) With the generous assistance of the ERP-Research Fund.

(3) The penicillin was kindly provided by the Hoechst color industries.